DATA EVALUATION RECORD

ETHABOXAM/090205
[LCG-30473]

STUDY TYPE: PRENATAL DEVELOPMENTAL TOXICITY STUDY - RABBIT
[OPPTS 870.3700b (§83-3b); OECD 414]

MRID NUMBERS 46490401 (Main Study), 46387807 (Range-finding)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1801 Bell Street
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 103-2005D

Primary Reviewer:
Donna L. Fefee, D.V.M.

Signature: Robert H. Ross for D.L. Fefee
Date: AUG 2 9 2005

Secondary Reviewers:
Carol S. Wood, Ph.D., D.A.B.T.

Signature: Carol S Wood
Date: AUG 2 9 2005

Robert H. Ross, M.S., Group Leader

Signature: Robert H. Ross
Date: AUG 2 9 2005

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: L.A. Wilson
Date: AUG 2 9 2005

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EPA Reviewer: Karlyn J. Bailey, M.S. **Signature:** Karl
Registration Action Branch 2, Health Effects Division (7509C) **Date** 4/25/06
EPA Work Assignment Manager: Ghazi Dannan, Ph.D. **Signature:** Ghazi Dannan
Registration Action Branch 3, Health Effects Division (7509C) **Date** 4/25/06
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DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Toxicity Study – Rabbit [OPPTS 870.3700b (§83-3b); OECD 414].

PC CODE: 090205 **DP BARCODE:**D313732

TEST MATERIAL (PURITY): Ethaboxam (LGC-30473, 97.5% a.i.)

SYNONYMS: *(RS)-N*-(α-cyano-2-thenyl)-4-ethyl-2-(ethylamino)-1,3-thiazole-5- carboxamide

CITATION: Gardner, T., H. Palmer, O. Green, et al. (1997) LGC-30473: study for effects on embryofoetal development in the New Zealand white rabbit by gavage administration. Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, England. Laboratory report number LKY 37/961723, April 10, 1997. MRID 46490401. Unpublished.

Gardner, T., H. Palmer, O. Green, et al. (1996) LGC-30473: a dose range finding study of effects in the pregnant New Zealand white rabbit by gavage administration. Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, England. Laboratory report number LKY 38/962365, November 5, 1996. MRID 46387807. Unpublished.

SPONSOR: LG Chemical Ltd, Taejon, Korea.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 46490401), Ethaboxam (LGC-30473, 97.5% a.i.) was administered to 20 mated female New Zealand White rabbits/dose by gavage in 1% methylcellulose at dose levels of 0, 25, 75, or 125 mg/kg bw/day on gestation days (GD) 6 through 28, inclusive. On GD 29, all surviving does were sacrificed and necropsied. Gravid uterine weight, corpora lutea count, the number and position of live fetuses, the number of early and late embryonic/fetal deaths, and number of aborted fetuses were recorded. All live fetuses were weighed, sexed, and subjected to external, visceral, and skeletal examinations, including evaluation of the brain via a slice taken through the line of the frontoparietal suture.

Two high-dose females were sacrificed (one each on GDs 15 and 16) after exhibiting prolonged inappetence beginning on GD 7-10 and poor body condition beginning on GD 12-13. High-dose does had a greater body weight loss during GD 6-8 (-73 g vs. -16 g for controls; N.S., not statistically significant), followed by compensatory increased body weight gain during GD 8-17 (145% of controls). Cumulative body weight gain over the dosing interval was similar to that of controls. Mid- and high-dose does had decreased mean daily food consumption during GD 6-7

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(81% and 70%; $p<0.05$ and $p<0.01$, respectively). There were no treatment-related effects on absolute body weight, corrected (for gravid uterus) body weight, or gross pathology. These effects are consistent with those observed in the range-finding study (see appendix) after exposure to LGC-30473. In the study, decreased food consumption was seen in treated groups compared to controls, as well as inappetence, body weight loss, and poor physical condition at 300 mg/kg/day.

The maternal LOAEL is 125 mg/kg bw/day, based on inappetence, decreased food consumption, and body weight loss. The maternal NOAEL is 75 mg/kg bw/day.

There were no treatment-related effects on live litter size, early or late embryonic/fetal deaths, or postimplantation loss. There were no treatment-related effects on fetal sex ratios or the mean fetal weight for the combined sexes. The total numbers of fetuses (and litters) evaluated in the control, low-, mid-, and high-dose groups were 172 (19), 133 (17), 170 (20), and 137 (16), respectively, and there were a total of 5 (4), 8 (7), 4 (3), and 4 (4) fetuses (litters) with malformations in these same respective groups.

The developmental LOAEL is not determined, and the developmental NOAEL is 125 mg/kg bw/day.

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement (OPPTS 870.3700b; OECD 414) for a developmental toxicity study in the rabbit.

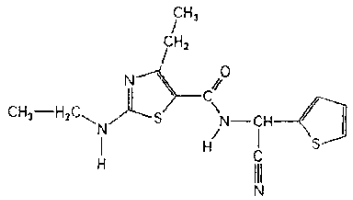
COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided for both the main study and the range-finding study.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. **Test material:** LGC-30473

Description:	Light brown powder; melting point: 185.2° C; water content: 0.3%; Molecular weight: 320.43
Batch #:	4-1
Purity:	97.5% a.i. [August 8, 1996; by sponsor] or 102.2% a.i. [March 14, 1997; by testing facility]
Compound Stability:	Expiration date not provided; expected to be stable for the duration of the study
CAS #of TGAI:	162650-77-3
Structure:	



2. **Vehicle and/or positive control:** The vehicle was 1% aqueous methylcellulose (lot/batch number and purity not provided). There was no positive control.

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3. Test animals:

Species:	Rabbit
Strain:	New Zealand White
Age/weight at study initiation:	Females: 15-25 weeks/3077-4174 g on GD 0; Males: no information was provided (females were supplied time-mated).
Source:	Harlan Interfauna Limited, Huntingdon, Cambridgeshire
Housing:	Individually in metal cages with solid stainless steel sides, back, and top, a stainless steel wire front, and a perforated aluminum floor panel.
Diet:	SDS STANRAB (P) SQC rabbit maintenance diet, *ad libitum*
Water:	Tap water, *ad libitum*
Environmental conditions:	**Temperature:** 14-22°C **Humidity:** 30-77% **Air changes:** Not reported **Photoperiod:** 10 hrs dark/14 hrs light. Per study report, "natural lighting in the room was supplemented by artificial light between 0700 and 2100 hours."
Acclimation period:	None; animals were supplied time-mated and arrived 6 days before dosing began.

B. PROCEDURES AND STUDY DESIGN:

1. **In life dates:** Start: May 7, 1996; End: June 13, 1996.

2. **Mating:** Females were naturally mated with males of proven fertility while at the supplier. Each doe was allowed to remain with the buck for at least one hour after mating was observed and was given an intravenous injection of Chorulon® (25 IU) afterwards. The day on which mating occurred was designated as gestation day (GD) 0. Matings were conducted on 5 separate days, and each batch of 16 animals was shipped to arrive at the testing facility on GD 0. The study report did not specify whether the males used were of the same strain as the females.

3. **Animal assignment:** Upon arrival, each batch of animals was evenly divided among the dose groups given in Table 1. The study report stated that the particular males used for mating and the derivation of the females were also evenly distributed across groups.

TABLE 1: Animal assignment

Group	Control	Low-Dose	Mid-Dose	High-Dose
Dose (mg/kg bw/day)	0	25	75	125
Number of Females	20	20	20	20

Data taken from text, p. 13, MRID 46490401.

4. **Dose selection rationale:** Dose levels were selected based on the results from a range-finding prenatal developmental toxicity study in New Zealand White rabbits (MRID 46387807; summarized in the Appendix), in which Ethaboxam (90.4% a.i.) was administered by gavage to groups of 6 time-mated females on GDs 6 through 28. Treatment at 300 mg/kg bw/day resulted in maternal weight loss and inappetence severe enough to necessitate the humane sacrifice of one animal and the removal of two others from treatment; there was also an abortion and a decrease in fetal body weight. Treatment-related effects at 150 mg/kg bw/day included decreased food consumption, and transient weight loss followed by impaired weight gain for the remainder of the study; however, absolute body weight was not significantly affected. At 75 mg/kg bw/day, there was transient weight loss and

subsequent compensatory increased weight gain during the remainder of gestation, and a slight, transient decrease in food consumption.

Dose levels of 0, 25, 75, and 125 mg/kg bw/day were selected for the main study with the expectation that the 25 mg/kg bw/day dose level would provide a NOAEL, and that the 75 and/or 125 mg/kg bw/day dose levels would result in maternal toxicity. The fact that the batch of test material used in the range-finding study was of a lower purity than the one used in the main study (90.4% a.i. vs. 97.5%) was also taken into consideration during dose selection.

5. **Dosage preparation and analysis:** Test material-vehicle suspensions were prepared weekly by grinding appropriate amounts of the test substance with a mortar and pestle, grinding a small amount of 1% aqueous methylcellulose (vehicle) into the powder to form a smooth paste, adding sufficient vehicle to form the required volume of suspension, and then using a Silverson mixer fitted with a fine screen. A magnetic stirrer was used to stir the dosing suspensions during dosing. Acceptable homogeneity and stability of the mixes were confirmed during an earlier study (MRID 46387806) in which LCG-30473 and dietary formulations contained nominal concentrations of the test article of 1mg/ml and 250 mg/ml. Data were not included in this report.

Results:
Homogeneity analysis: Confirmed in earlier study (MRID 46387806). At nominal concentrations of 1mg/ml and 250 mg/ml, homogeneous suspensions in 1% MC formulation were maintained for up to 2 hours while magnetically stirred.

Stability analysis: Confirmed in earlier study (MRID 46387806). It was established that diets could be stored in the dark at ambient temperature for 2 days; refrigerated for 8 days.

Concentration analysis: Absence of the test material was confirmed in the vehicle. Mean concentrations of the low-, mid-, and high-dose suspensions were 100.6%, 99.3%, and 97.5% of nominal, respectively, and all of the measured concentrations of the individual samples were within ±3% nominal.

The information provided and the analytical data indicated that the mixing procedure was adequate and the variance between nominal and actual dosage to study animals was acceptable.

6. **Dosage administration:** All doses were administered once daily by gavage, on gestation days 6 through 28, in a volume of 5 mL/kg of body weight/day. Dose volumes were based on the individual body weight at the time of the most recent body weight determination. Dosing was done at approximately the same time each day, to the extent possible.

C. OBSERVATIONS:

1. **Maternal observations and evaluations:** The animals were checked daily for mortality or clinical signs. Body weight was recorded on GDs 0, 2, 6, 8, 10, 12, 14, 17, 20, 23, 26, and 29, and food consumption was measured over the intervals in between the days on which the

animals were weighed. On GD 29, all surviving does were sacrificed via intravenous injection of pentobarbitone sodium and subjected to a gross necropsy. Gravid uterine weight, corpora lutea count, the numbers and positions of live fetuses, early embryonic/fetal deaths (only placental remnants visible), late embryonic/fetal deaths (both placental and embryonic remnants visible), and aborted fetuses (only implantation site scars visible) were recorded. There was no mention of the use of ammonium sulfide or a similar technique to detect very early resorptions in any uterus without gross evidence of implantation.

Animals that died or were sacrificed moribund were subjected to gross necropsy. Does were not sacrificed ahead of schedule following abortion or early delivery unless it was necessary for humane reasons.

2. **Fetal evaluations:** All live fetuses were examined externally. Following euthanasia via intrathoracic pentobarbitone sodium injection, the fetuses were weighed, subjected to visceral examination by fresh dissection, and sexed internally. The carcasses were skinned, eviscerated, and fixed in 74 OP industrial methylated spirit. The fixed heads were sliced through the line of the frontoparietal suture for evaluation of the brain, and the carcasses were then cleared, stained, and subjected to skeletal examination. Further evaluation by histopathology or other alternative procedure(s) was done as needed to clarify initial observations.

Morphological alterations were classified as malformations (changes that are rare and/or probably lethal), anomalies (minor variations that are detected relatively frequently), or variants (alternative stuctures that occur regularly in the control population either as permanent structures or as transient stages of development).

D. DATA ANALYSIS:

1. **Statistical analyses:** Body weight changes and food consumption were analyzed either using ANOVA, followed by Williams' test (when the data had homogeneous variance) or using the Kruskal-Wallis test, followed by Shirley's test (when the data had non-homogeneous variance). Fetal variants and litter data (numbers of corpora lutea, implantations, *in utero* deaths, and live young, litter and gravid uterine weights, fetal weight, fetal sex ratio) were analyzed using the Kruskal-Wallis test, followed by Shirley's test. If ≥ 75% of the values were identical, the data were analyzed using the Fisher's exact test. In analyzing the litter data and fetal variants, the litter was considered to be the unit of statistical analysis.

The incidence and distribution within litters of pre-implantation loss, *in utero* deaths, and fetal malformations and anomalies were analyzed using the Linear by Linear Association test in a step down fashion. If no statistical significance was found, the data were also analyzed for non-linear responses using the Kruskal-Wallis test, followed by pair-wise permutation tests (Gibbons, 1985) if the results of the Kruskal-Wallis test were significant at the 1% probability level.

Differences from the control were considered significant at the 5% probability level.

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2. **Indices:** The following indices were calculated by the reviewer:

Preimplantation loss (%) = 100×[(total # corpora lutea-total # implants)/total # corpora lutea]

Postimplantation loss (%) = 100×[(total # implants-total # live fetuses)/total # implants]

3. **Historical control data:** Historical control data were not provided.

II. RESULTS:

A. MATERNAL TOXICITY:

1. **Mortality and clinical observations:** There were a total of five unscheduled sacrifices during the study. Two high-dose females were sacrificed (one each on GDs 15 and 16) after exhibiting prolonged inappetence beginning on GD 7-10 and poor body condition beginning on GD 12-13; these deaths were considered treatment-related. One high-dose female was sacrificed on GD 6, and one low-dose female was sacrificed on GD 23 as the result of gavage error. One low-dose doe was sacrificed on GD 27 following early delivery of 2 dead fetuses on GD 26 with subsequent observations of lethargy and unsteady gait on GD 27, and the cause of death was determined to be the presence of 11 dead fetuses *in utero*. One control delivered on GD 29, and a second low-dose doe aborted but the data do not include the gestation day on which this occurred. The abortions in the control and low-dose groups, and the abortion-related death of the low-dose doe were not considered treatment-related.

   All treated animals had orange urine which was noted beginning on GD 7-9 and on most days during the remainder of the study. Among surviving does, reduced food consumption/fecal output of greater than three days duration was noted.

2. **Body weight:** Selected maternal body weight data are given in Table 2. The mean absolute body weight of all treated groups was similar to that of controls throughout the study. Although statistical significance was not attained, greater weight loss by high-dose does during GD 6-8 was considered both treatment-related and biologically significant. Compensatory increased body weight gain by this group during GD 8-17 resulted in an overall GD 6-29 (or treatment interval) body weight gain that was similar to that of controls. The mean cumulative body weight gain of the high-dose group was greater than that of controls, both with and without correction for gravid uterine weight, and this was mostly due to the group's greater body weight gain during GD 0-6. The body weight changes of the low- and mid-dose groups differed greatly from those of controls during some of the 2- to 3-day measuring intervals, but a dose-response pattern was not evident, and the differences were not consistent over time.

TABLE 2: Maternal body weight data [a]				
Gestation Day or Interval	Dose in mg/kg bw/day (# of Does)			
	Control (19)	25 (17)	75 (20)	125 (16)
Absolute body weights (g)				
GD 0	3656	3569	3591	3586
GD 6	3820	3765	3777	3842
GD 8	3804	3770	3762	3769
GD 17	3986	3930	3957	4033
GD 29	4222	4145	4170	4257
Gravid uterine weight	552.3	481.1 (87) [b]	530.7	542.1
Body weight gains (g)				
GD 0-6 (Pre-treatment)	165	196 (119)	187 (113)	255 (155)
GD 6-8	-16	5	-15	-73
GD 8-17 [c]	182	160 (88)	195 (107)	264 (145)
GD 17-29 [c]	236	215 (91)	213 (90)	224 (95)
GD 6-29 (Treatment)	402	380	393	415
GD 0-29 (Gestation) [c]	566	576	579	671 (119)
Corrected BW Gain [d]	14	95	48	129

Data taken from Tables 2 and 4, pp. 24 and 26, MRID 46490401.

[a] Standard deviations were not reported.

[b] Numbers in parentheses equal percent of control; calculated by the reviewer.

[c] Calculated by the reviewer using group mean body weight values; not subjected to statistical analysis.

[d] Corrected BW Gain = body weight gain during GD 0-29 minus gravid uterine weight, rounded to the nearest whole gram.

3. **Food consumption:** Transient dose- and treatment-related decreases in mean daily food consumption occurred at all dose levels during GD 6-7 (87%, 81%* and 70%** of controls in ascending dose order; * $p<0.05$, ** $p<0.01$). Throughout the remainder of the study, the mean food consumption of the treated groups was generally similar to that of controls, and any differences that did occur lacked a dose response and were not considered treatment-related.

4. **Gross pathology:** Treatment-related observations were limited to orange staining of the fur in 6 low-dose, 15 mid-dose, and 12 high-dose animals (vs. no controls), and dark orange urine in the urinary bladders of the two high-dose decedents. These findings were obviously related to the in life observations of orange urine. Other common findings (in all groups) included fur loss in various locations, and subcapsular cortical scarring of the kidneys, which was noted in 1-4 animals from each group with no evidence of a dose response.

5. **Cesarean section data:** Data collected at cesarean section are summarized in Table 3. There were no treatment-related effects on live litter size, early or late embryonic/fetal deaths, or

postimplantation loss. There were no treatment-related effects on fetal sex ratio or the mean fetal weight for the combined sexes.

TABLE 3. Cesarean section observations [a]

Observation		Dose (mg/kg bw/day)			
		0	25	75	125
# Animals assigned (mated)		20	20	20	20
# Animals pregnant [Pregnancy Rate]		20 [100%]	20 [100%]	20 [100%]	18 [80%]
Maternal wastage:					
# Deaths/moribund sacrifices		0	2 [b]	0	3
# Aborted or delivered early		1	2 [b]	0	0
# Litters with total resorptions		0	0	0	0
# Litters for evaluation		19	17	20	16
Corpora lutea:	Mean # per doe	11.5	10.6	10.7	10.6
	Total # per group [c]	218	180	213	169
Implantations:	Mean # per doe	9.7	8.6	9.6	9.8
	Total # per group [c]	185	146	191	157
Live fetuses:	Mean # per doe	9.1	7.8	8.5	8.6
	Total # per group	172	133	170	137
Embryonic/fetal deaths:	Mean # per doe				
	Early	0.3	0.5	0.7	0.8
	Late	0.4	0.2	0.4	0.4
	Total	0.7	0.8	1.1	1.3
Embryonic/fetal deaths:	Total # per group [c]				
	Early	5	9	14	13
	Late	8	4	7	7
	Total	13	13	21	20
Embryonic/fetal deaths: # [%] Does with ≥1 [c]		9 [47.4%]	9 [52.9%]	12 [60.0%]	12 [75%]
Preimplantation loss (%) [d]		15.1	18.9	10.3	7.1
Postimplantation loss (%) [d]		7.0	8.9	11.0	12.7
Mean fetal weight (g)		42.5	44.4	44.2	43.9
Sex Ratio (Mean % Male)		48.5	44.4	49.1	53.3

Data taken from Table 4, Table 6, and Appendix 4, pp. 26, 28, and 50-53, respectively, MRID 46490401.

[a] Values given as Mean ± Standard Deviation, where appropriate.

[b] One low-dose doe that aborted was later sacrificed for humane reasons and is included in both categories.

[c] Compiled from individual data by reviewer.

[d] Calculated by reviewer and not analyzed statistically.

B. <u>DEVELOPMENTAL TOXICITY</u>: The total numbers of fetuses (and litters) evaluated in the control, low-, mid-, and high-dose groups were 172 (19), 133 (17), 170 (20), and 137 (16), respectively, and there were a total of 5 (4), 8 (7), 4 (3), and 4 (4) fetuses (litters) with malformations in these same respective groups. All reported fetal malformations and selected fetal anomalies are given in Tables 4a and 4b, respectively. Observations from the external examinations were not reported separately and the morphological data from fetuses with malformations were reported without categorization of the observations as visceral, skeletal, or external. All reported fetal malformations and selected fetal variations are given in Tables 4a and 4b, respectively.

1. **External examination:** External malformations were noted in one fetus from each of the control and high-dose groups. Cleft palate was noted in both fetuses and was the only abnormal finding in the high-dose fetus, while the control fetus had additional external malformations involving the craniofacial midline.

2. **Visceral examination:** Visceral malformations were found in 2 (2), 4 (4), 4 (3), and 3 (3) fetuses (litters) from the control, low-, mid-, and high-dose groups, respectively. All of the individual malformations were noted at very low incidences, and none were considered treatment-related. Visceral anomalies included corneal opacity, small eyes, anomalous cervicothoracic arteries or systemic/pulmonary arteries, absent intermediate lung lobe, and bilobed or bifurcated gall bladder. All occurred at low incidences and without a dose response; therefore none were considered treatment-related.

3. **Skeletal examination:** Skeletal malformations were found in 4 (3), 5 (4), 1 (1), and 0 (0) fetuses (litters) from the control, low-, mid-, and high-dose groups, respectively. All of the individual malformations were noted at very low incidences, and none were considered treatment-related. The most common skeletal anomalies from fetuses without malformations included the following: sutural bone(s) in the skull; bridge of ossification from jugal to maxilla; irregular ossification of cranial bones or cervical vertebral elements; cervical rib(s); and incomplete ossification of the digits. All were present at similar incidences in the treated and control groups and without a dose response; therefore none were considered treatment-related. The mean litter percentages of fetuses with 12/13 ribs, normal sternebrae, and total variant sternebrae were comparable among groups.

TABLE 4a. Fetal malformations [Fetal (Litter) incidences]				
Observations [a]	Dose (mg/kg bw/day)			
	0	25	75	125
Total number examined	172 (19)	133 (17)	170 (20)	137 (16)
Total number affected	5 (4)	8 (7)	4 (3)	4 (4)
External Malformations				
Cebocephaly and single naris with absent nasolabial sulcus	1 (1) [b]	0	0	0
Cleft palate	1 (1) [b]	0	0	1 (1)
Visceral Malformations				
Hydrocephaly	1 (1) [b]	1 (1)	0	0
Malformed cervicothoracic arteries	0	0	2 (1) [h i]	1 (1)
Malformed systemic/pulmonary arteries	1 (1)	2 (2) [e f]	3 (2) [h i]	2 (2) [k]
Interventricular septal defect	0	1 (1) [e]	0	1 (1) [k]
Small ventricle	0	0	1 (1) [i]	0
Incomplete inferior vena cava with persistent posterior cardinal vein	0	1 (1) [f]	0	0
Umbilical hernia	0	1 (1)	0	0
Kidney - cystic tubules with capsule adhered to ovary	0	0	1 (1) [j]	0
Number with visceral malformations	2 (2)	4 (4)	4 (3)	3 (3)
Skeletal Malformations				
Flattened cranium, protruding occipital region, and lumbosacral spina bifida	0	1 (1)	0	0
Absent incisors and absent premaxillae	1 (1) [b]	0	0	0
Fused upper incisors and premaxillae	1 (1) [c]	0	0	0
Partially fused frontals	1 (1)	0	0	0
Partially fused parietals	0	1 (1)	0	0
Cervical vertebrae - multiple irregularities with scoliosis	0	1 (1) [f]	0	0
Thoracic vertebrae - multiple irregularities	1 (1) [d]	2 (2) [f g]	0	0
Thoracic hemivertebra	1 (1) [c]	0	0	0
Thoracic scoliosis, minimal	2 (2) [c d]	1 (1) [f]	0	0
Ribs - absent	1 (1) [c]	2 (2) [g]	0	0
Ribs -partially fused	0	1 (1) [f]	0	0
Ribs - multiple irregularities	1 (1) [d]	0	0	0
Lumbar vertebrae - multiple irregularities with scoliosis	0	0	1 (1) [j]	0
Number with skeletal malformations	4 (3)	5 (4)	1 (1)	0 (0)

Data taken from Table 6 and Appendix 7, pp. 28 and 62-68, respectively, MRID 46490401.

[a] Some observations may be grouped together.

[b–k] Multiple observations that were from the same fetus are indicated by identical superscripts.

TABLE 4b. Fetal anomalies [Fetal (Litter) incidences]				
Observations [a]	Dose (mg/kg bw/day)			
	0	25	75	125
Total number examined [b]	167 (19)	125 (17)	166 (20)	133 (16)
Visceral Anomalies				
Corneal opacity	1 (1)	1 (1)	0	1 (1)
Eyes, small	0	1 (1)	0	0
Cervicothoracic arteries anomalous	2 (2)	3 (3)	1 (1)	1 (1)
Systemic/pulmonary arteries anomalous	1 (1)	0	0	1 (1)
Intermediate lung lobe absent	1 (1)	2 (2)	1 (1)	1 (1)
Gall bladder bilobed/bifurcated	0	1 (1)	2 (2)	1 (1)
Number affected	5 (5)	8 (7)	4 (4)	5 (5)
Skeletal Anomalies				
Sutural bone(s) in the skull	1 (1)	4 (3)	7 (5)	2 (1)
Bridge of ossification from jugal to maxilla	3 (2)	4 (4)	6 (4)	7 (5)
Irregular ossification of cranial bones	3 (3)	2 (2)	6 (6)	1 (1)
Irregular ossification of cervical vertebral elements	2 (2)	4 (4)	6 (5)	4 (3)
Cervical rib(s)	4 (3)	4 (2)	4 (4)	1 (1)
Digits - incomplete ossification	3 (3)	3 (2)	4 (2)	2 (2)
Number affected	19 (12)	21 (10)	33 (17)	18 (10)

Data taken from Tables 7 and 8, pp. 29 and 30, respectively, MRID 46490401.

[a] Some observations may be grouped together.

[b] Fetuses with malformations are excluded.

III. DISCUSSION AND CONCLUSIONS:

A. **INVESTIGATORS' CONCLUSIONS:** According to the study authors, the observations of orange-colored urine and orange stained fur on the paws were due to excretion of the parent material or its metabolites. The study authors concluded that adverse treatment-related maternal effects included decreased food consumption at the 75 and 125 mg/kg bw/day dose levels, with additional adverse effects on maternal body weight and survival occurring at the 125 mg/kg bw/day dose level. According to the study authors, there were no significant treatment-related effects on the does at the 25 mg/kg bw/day dose level, and no adverse effects on embryofetal development were seen at any of the dose levels tested. The study authors concluded that the maternal NOAEL for the study was 25 mg/kg bw/day and that the NOAEL for embryofetal development was 125 mg/kg bw/day.

B. REVIEWER COMMENTS:

1. **Maternal toxicity:** The reviewer agrees that there were transient decreases in food consumption observed at 75 and 125 mg/kg bw/day, and body weight loss and moribundity noted at 125 mg/kg bw/day; however, the decreases in food consumption alone at 75 mg/kg bw/day are not considered adverse. Evidence of maternal toxicity was seen at 125 mg/kg/day, where decreases in food consumption was accompanied by body weight loss and moribundity due to innappetence. The reviewer agrees that the orange-colored urine and orange staining observed during the study were related to excretion of the parent compound and/or its metabolites, and these treatment-related findings are not considered adverse.

   The maternal LOAEL is 125 mg/kg bw/day, based on decreased food consumption, inappetence, and body weight loss . The maternal NOAEL is 75 mg/kg bw/day.

2. **Developmental toxicity:**

   a. **Deaths/resorptions:** Maternal treatment did not result in an increase in fetal deaths or resorptions.

   b. **Altered growth:** Fetal body weight was similar in the treated and control groups, and there was no evidence of delayed ossification.

   c. **Developmental variations:** Treatment did not result in an increased incidence of fetal developmental anomalies or variants.

   d. **Malformations:** The total fetal and litter incidences of malformations were not significantly increased in the treated groups, and all individual malformations occurred at very low incidences.

   The developmental LOAEL is not determined and the NOAEL is 125 mg/kg bw/day.

C. STUDY DEFICIENCIES: None

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APPENDIX

APPENDIX: Prenatal Developmental Toxicity Study – Rabbit; Range-finding.

TEST MATERIAL (PURITY): LGC-30473 (Ethaboxam; Batch no. 2-3, 90.4% a.i.)

CITATION: Gardner, T., H. Palmer, O. Green, et al. (1996) LGC-30473: a dose range finding study of effects in the pregnant New Zealand white rabbit by gavage administration. Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, England. Laboratory report number LKY 38/962365, November 5, 1996. MRID 46387807. Unpublished.

SUMMARY: In a range-finding developmental toxicity study (MRID 46387807), Ethaboxam (LGC-30473, 90.4% a.i.) was administered to 6 mated female New Zealand White rabbits/dose by gavage in 1% methylcellulose at dose levels of 0, 75, 150, or 300 mg/kg bw/day on gestation days (GDs) 6 through 28, inclusive. On GD 29, all surviving does were sacrificed and necropsied. Gravid uterine weight, corpora lutea count, the numbers and positions of live fetuses, early and late embryonic/fetal deaths, and aborted fetuses were recorded. All live fetuses were weighed, sexed, and subjected to external and visceral examinations.

One control animal was sacrificed following gavage error (tracheal intubation). One high-dose female was sacrificed on GD 19 due to exhibiting poor/thin physical condition, unsteady gait, and body weight loss of almost 700 g. Two high-dose animals were removed from treatment on GD 22 due to prolonged and severe inappetence (consuming less than 7 g food/day over the preceding 8-10 days), and one of these aborted on GD 20-21. All treated animals had orange-colored urine beginning on GD 7, with orange-stained fur noted on some animals. High-dose does lost considerable weight during the treatment interval (-264 g), with the most pronounced change occurring during GD 6-12 (-233 g), and significantly decreased absolute body weight was noted at this dose level during GD 14-29 (86-91% of controls). Low- and mid-dose does had transient weight loss during GD 6-8 (respectively -8 and -112 g. vs. +87 g for controls). Low-dose does had compensatory increased weight gain during the remainder of gestation, which resulted in an overall GD 6-29 weight gain similar to that of controls. Mid-dose does had decreased body weight gain during GD 8-29 (67% of controls). Absolute body weights of the low- and mid-dose groups were not significantly affected by treatment. Treatment-related decreases in food consumption were seen at all treated groups beginning on GD 6 (74-87%, 55-86%, and 29-87% of controls). For high-dose does, the most marked differences occurred during GD 6-19, and improvement was seen by GD20. The mid- and low-dose does showed recovery by GD 20 and GD 14, respectively.

The maternal LOAEL is 75 mg/kg bw/day, based on decreased food consumption and transient body weight loss. The maternal NOAEL is not determined.

As previously mentioned, one high-dose female aborted. Decreased fetal body weight at the highest dose level (87%) was considered to be treatment-related. There were no total litter resorptions, and there were no treatment-related effects on postimplantation loss, mean numbers of resorptions and fetuses per litter, or fetal sex ratios. In the control, low-, mid-, and high-dose groups, a total of 50 (5), 45 (6), 46 (5), and 30 (4) fetuses and litters were evaluated. Malformations were noted in one high-dose fetus (umbilical hernia) and one mid-dose fetus (incomplete inferior vena cava with persistent right posterior cardinal vein). Abnormalities were

(incomplete inferior vena cava with persistent right posterior cardinal vein). Abnormalities were noted in 0 (0), 3 (3), 6 (2), and 5 (3) fetuses (and litters) from the control, low-, mid-, and high-dose groups, respectively. Small size and variation in origin of arteries arising from the aortic arch were each seen in 2 (2) high-dose fetuses (litters), and bilateral corneal opacity was seen in 5 (1) mid-dose fetuses (litters). The remaining abnormalities occurred in single fetuses.

The developmental LOAEL is 300 mg/kg bw/day, based on abortion and decreased fetal weight. The developmental NOAEL is 150 mg/kg bw/day.

Based on the results of this study, dose levels of 0, 25, 75, and 125 mg/kg bw/day were selected for the main study.

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